IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 99-371)

PATENT

In re Application of: Thomason et al.	)	
	)	
Serial No.: 09/391,861	)	**Before the Examiner: F. G. Sajjadi**
	)	
Filed: September 7, 1999	)	**Group Art Unit: 1633**
	)	
For: Fibroblast Growth Factor-Like Polypeptides	)	**Confirmation No.: 9209**
	)	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. MURIELLE VENIANT-ELLISON UNDER 37 C.F.R. § 1.132

I, Murielle Veniant-Ellison, hereby declare:

1. I hold a D.E.A (U.S. equivalent to Master's degree) in pharmacology from the University of Dijon, France, which I received in 1989, and a Ph.D. in pharmacology from the University of Dijon, which I received in 1992. I have been engaged in research since 1988 and in drug development research for more than ten years. For the last seven years I have worked to develop therapeutics for treating metabolic disorders such as diabetes and obesity. My *curriculum vitae* is attached hereto as Appendix A.

2. I have been employed at Amgen Inc. for seven years, where I am currently a Scientific Director in therapeutic area of metabolic disorders. During this time I have been responsible for preclinical pharmacology for Amgen's diabetes drug development programs, including FGF-21. Some results of Amgen's analysis performed with human and murine FGF-21 are shown in Appendix B.

3. Using RT-PCR experiments, human FGF-21 mRNA was shown to be highly expressed in liver (*see* Appendix B, page 1). Using *in situ* hybridization experiments, mouse FGF-21 was shown to be mainly expressed in liver and pancreas (*see* Appendix B, page 1).

4. As shown in U.S. Patent Application Serial No. 09/391,861 ("the Application"), transgenic mice overexpressing FGF-21 had reduced body and liver weights as compared to wild-

type mice (*see* Appendix B, page 2; *see, e.g.*, page 4, lines 22-28 of Application). These mice are resistant to aging-related obesity and type 2 diabetes.

5. When *ob/ob* mice (a well-characterized mouse model of diabetes and obesity broadly used in the therapeutic area of metabolic disorders) are injected with native recombinant FGF-21 (the mature form of the human and murine FGF-21 disclosed in the Application), the mice showed a statistically significant reduction in blood glucose levels and in body weight as compared with *ob/ob* mice injected with phosphate buffered saline (PBS) (*see* Appendix B, page 3).

6. The effect of murine FGF-21 on diabetes and obesity was studied in Diet Induced Obesity (DIO) mice, a well-characterized mouse model of obesity in which mice are fed a high fat diet for twelve weeks prior to starting the treatment and then are kept on the high fat diet during treatment. In these experiments, DIO mice were injected with murine FGF-21 for six weeks (at low medium and high doses). Treated mice were found to have statistically significantly decreased body weight in a dose response manner. Also, the histology of the livers of the mice treated with FGF-21 looked similar to the livers of the mice fed a normal chow diet. In contrast, the liver appearance (where white color is indicative of fat accumulation) and the amount of body fat in DIO mice injected with PBS was greater than in FGF-21 treated mice (*see* Appendix B, page 4).

7. DIO mice injected with high and medium doses of murine FGF-21 for three weeks showed statistically significant reductions in fasting glucose, insulin, free fatty acid, cholesterol and triglyceride levels, all of which are physiological parameters associated with diabetes and obesity (*see* Appendix B, page 5).

8. DIO mice injected with murine FGF-21 for six weeks showed a striking reduction in liver neutral lipid levels as compared with DIO mice injected with PBS (*see* Appendix B, page 6), which suggests to me that FGF-21 can be used to treat conditions such as diabetes and obesity where fat accumulation is of concern.

9. DIO, *ob/ob*, and lean mice injected with murine FGF-21 showed an improvement in glucose tolerance (*see* Appendix B, page 7), which suggests to me that FGF-21 can be used to treat diabetes.

10. Administration of human FGF-21 to mice decreased blood glucose levels and improved glucose tolerance for at least 24 hours after administration of FGF-21 was stopped,

indicating that glucose levels can be controlled for an extended period of time (*see* Appendix B, page 8).

11. I have reviewed the "Declaration of Dr. David Ornitz under 37 C.F.R. § 1.132" and agree with Dr. Ornitz' conclusions.

12. I have reviewed the Application, and based on my understanding of the Application, I believe it provides support for the therapeutic use of FGF-21 (which is referred to as FGF-like molecules in the Application) for the treatment of metabolic diseases such as diabetes and obesity. In addition to the factors described in Dr. Ornitz' Declaration, my belief is based on the following factors:

12(a). First, the Application describes that FGF-21 is expressed primarily in the liver with lower levels of expression in lung and fetal liver (*see, e.g.*, page 4, line 39 to page 5, line 1; page 80, lines 14-16; page 80, lines 2-5; and Figures 4A-4C of Application). Gene expression pattern is an important tool for drug discovery. Specifically, the liver is one of the major organs involved in the regulation of metabolic parameters, and more specifically in diabetes. In the case of FGF-21, the expression pattern is very indicative of its potential involvement in diabetes.

12(b). Second, the Application describes that transgenic mice overexpressing FGF-21 show, among other things, a reduction in body weight and a reduction in liver weight as a percent of body weight (*see, e.g.*, page 4, lines 22-26 of Application). It is well known that accumulation of lipids in the liver is linked to insulin resistance, and type 2 diabetes. Correlated with this are liver tissue mass, adiposity, and overall body weight. It is known that fat accumulates in the liver when the rate of delivery of fatty acids to hepatocytes exceeds the metabolic processing capacity. Disturbances in mitochondrial ß-oxidation can result in the accumulation of triglycerides in the liver. Liver accumulation of fat in patients with type 2 diabetes or with insulin resistance syndrome is mainly related to increased lipolysis of adipose tissue, with an increased flux of free fatty acids to the liver that exceeds the liver's capacity to export very low density lipoproteins. The fact that body weights and liver weights of the transgenic mice overexpressing FGF-21 are reduced is indicative of an improvement in fat distribution in the body (naturally occurring with age) and specifically, in the liver, explaining resistance to diabetes.

12(c). Third, the Application describes that FGF-21 polypeptides can be used therapeutically to treat diabetes or fat deposition in the treatment of obesity (*see, e.g.*, page 5, lines 15-16 and 27 of Application).

13. Based on the expression of FGF-21 in the liver, the reduction in liver weight in transgenic mice overexpressing FGF-21, and the description in the Application that FGF-21 molecules can be used therapeutically to treat diabetes or fat deposition in the treatment of obesity, as well as my seven years of experience in developing therapeutics for the treatment of metabolic disorders such as diabetes and obesity, I agree with Dr. Ornitz' conclusions and I too would have understood that the FGF-21 molecules described in the Application would have therapeutic use in the treatment of diabetes or obesity.

14. Moreover, my work with FGF-21 indicates that the FGF-21 molecules described in the Application in fact exhibit therapeutic potential for treating diabetes or obesity.

15. All of the statements I made herein are truthful and made of my own volition. I understand that willful false statements may subject me to fines, imprisonment or both, pursuant to Section 1001 of Title 18 of the United States Code.

Signed: Murielle Veniant Ellison
Murielle Veniant-Ellison, Ph.D.

Dated: 01/02/2008

APPENDIX A

CURRICULUM VITAE

Murielle Véniant

EDUCATION

1983-1986	University of Dijon, Dijon, France; DEUG B in biology.
1986-1987	University of Dijon, Dijon, France; LICENCE in molecular biology.
1987-1988	University of Dijon, Dijon, France; MAITRISE in animal physiology.
1988-1989	University of Dijon, Dijon, France; DEA in pharmacology.
1989-1992	University of Dijon, Dijon, France (laboratory work performed at Hoffmann La Roche, Basel, Switzerland). Ph.D. awarded March 1992. Title: Pharmacologic evaluation of a new calcium antagonist Ro 40-5967: effects in normal rats, in rats with heart failure and in hypertensive rats (SHR and 2K-1C rats).

PROFESSIONAL EXPERIENCE

April 1992– Dec 1992	Hoffmann La Roche, Basel, Switzerland. Postdoctoral fellow under the supervision of Professor Jöel Ménard and Dr. Jean-Paul Clozel. Subject: Effects of the endothelin on blood pressure maintenance using endothelin antagonist.
1993–1995	Center for Genome Research. Postdoctoral fellow under the supervision of Dr. John Mullins, supported by INSERM grant from 1993 to 1994. Project: Role of the renin angiotensin system in hypertension using molecular biology and transgenic technology.
1994–1995	Teaching, University of Edinburgh "Honors endocrine pharmacology" Lecture in renal hypertension for students of B.Sc. (Pure science) and B.Sc. (Medical science). Chairperson in pharmacology to Ph.D. students (discussion club) at Centre of Genome Research, Edinburgh, UK.
1995– July 1997	Gladstone Institute of Cardiovascular Disease, San Francisco, USA. Postdoctoral Fellow under the supervision of Dr. Stephen Young. Project: Role of apolipoprotein B100 and apolipoprotein B48 in different models of knockout mice.
July 1997–March 2000	Gladstone Institute of Cardiovascular Disease, San Francisco, USA. Staff Research Investigator. Project: Function of apolipoprotein B in the heart.

April 2000– April 2001: Amgen Inc., Thousand Oaks, USA. Research Scientist I, Metabolic Disorders.

April 2001– March 2002: Amgen Inc., Thousand Oaks, USA. Research Scientist II, Metabolic Disorders.

March 2002– March 2004: Amgen Inc., Thousand Oaks, USA. Research Scientist III, Metabolic

Disorders.

March 2004– March 2006: Amgen Inc., Thousand Oaks, USA. Research Scientist IV/Principle scientist, Metabolic Disorders.

March 2006– present: Amgen Inc., Thousand Oaks, USA. Scientific Director, Metabolic Disorders.

HONORS, AWARDS, AND FELLOWSHIPS

1992	Young Investigators Award, European Hypertension Association
1993	Travel Award, American Hypertension Association
1993–1994	Mobility Award for Postdoctoral Research Abroad, INSERM, France
1998-2000	New Investigator Award, Principal Investigator, Tobacco-Related Disease Research Program ($400,000)

PUBLICATIONS

1. Clozel, J.P., **Véniant, M.**, and Osterrieder, W. (1990). The structurally novel Ca^{2+} channel blocker Ro 40-5967, which binds to the [3H] desmethoxyverapamil receptor, is devoid of the negative inotropic effects of verapamil in normal and failing rat hearts. Cardiovasc. Drugs Ther. 4:731-736.
2. **Véniant, M.**, Clozel, J.P., Hess, P., and Wolfgang, R. (1991). Ro 40-5967, in contrast to diltiazem, does not reduce left ventricular contractility in rats with chronic myocardial infarction. J. Cardiovasc. Pharmacol. 17: 277-284.
3. **Véniant, M.**, Clozel, J.P., Hess, P., and Wolfgang, R. (1991). Hemodynamic profile of Ro 40-5967 in conscious rats: Comparison with diltiazem, verapamil and amlodipine. J. Cardiovasc. Pharmacol. 18 (suppl. 10): S55-S58.
4. Clozel, J.P., **Véniant, M.**, Hess, P., and Sprecher, U. (1991). Effects of two angiotensin converting enzyme inhibitors and hydralazine on coronary circulation in hypertensive rats. Hypertension 18 (suppl II): 8-14.
5. **Véniant, M.**, Clozel, J.P., Hess, P. and Fischli, W. (1992). Effects of renin-angiotensin blockade in guinea pigs. Hypertension 19: 255-262.
6. **Véniant, M.**, Clozel, J.P. and Fischli, W. (1992). Mechanism of the potentiation by angiotensin converting enzyme inhibition of intradermal bradykinin in guinea pig: Comparison with renin inhibition and measurement of bradykinin degradation in blood. J. Hypertens. 10: 155-160.
7. **Véniant, M.**, Clozel, J.P., Kuhn, H. and Clozel, M. (1992). Protective effect of cilazapril on cerebral circulation. J. Cardiovasc. Pharmacol 19 (suppl. 6): S94-S99.
8. **Véniant, M.**, Clozel JP, Heudes D, Banken L, and Ménard J (1993). Effects of Ro 40-5967 a new calcium antagonist and enalapril on cardiac remodeling in renal hypertensive rats. J. Cardiovasc. Pharmacol . 21: 544-551.
9. Eng, E., **Véniant, M.**, Floege, J., Fingerle, J., Alpers, C. E., Ménard, J., Clozel, J.P., and Johnson, R. (1994). Renal proliferative and phenotypic changes in rats with two-kidney, one-clip Goldblatt model of hypertension. Am. J Hypertens. 7: 177-185.
10. **Véniant, M.**, Heudes, D., Clozel, J.P., Bruneval, P., and Ménard, J. (1994). Calcium blockade versus ACE inhibition in clipped and unclipped kidneys of 2K-1C rats. Kidney Int. 46: 421-429.

11. **Véniant, M.**, Clozel, J.P., Hess, P., and Clozel, M. (1994). Endothelin plays a role in the maintenance of blood pressure in normotensive guinea pigs. Life Sci. 55: 445-454.

12. **Véniant, M.**, Gray, G., Heudes, D., Ménard, J., and Clozel, J.P. (1995). Structural changes and cyclic GMP content of the aorta following calcium antagonist or ACE inhibition in renovascular hypertensive rats. J. Hypertens. 13: 731-737.

13. **Véniant, M.**, Whitworth, C., Ménard, J., Sharp, M.G.F., and Mullins, J.J. (1995). Developmental studies demonstrate age-dependent elevation of renin activity in TGR(mRen2)27 rats. Am. J. Hypertens. 8: 1167-1176.

14. Whitworth, C., **Véniant, M.**, Firth, J.D., Cumming, A.D., and Mullins, J.J. (1995). Endothelin in the kidney in malignant phase hypertension. Hypertension; 26: 925-931.

15. Clozel, J.P., **Véniant, M.**, Sprecher, U., and Fischli, W. (1995). Acute hemodynamic effects of Ciprokiren, a novel renin inhibitor, in sodium-depleted dogs. J . Cardiovasc. Pharmacol. 26: 674-677.

16. McCormick, S.P.A., Ng, J.K., **Véniant, M.**, Borén, J., Pierotti, V., Flynn, L.M., Grass, D.S., Connolly, A., and Young, S.G. (1996). Transgenic mice that overexpress mouse apolipoprotein B: evidence that the DNA sequences controlling intestinal expression of the apolipoprotein B gene are distant from the structural gene. J. Biol. Chem. 271:11963-11970.

17. Farese, R.V., **Véniant, M.**, Cham, C.M., Flynn, L.M., Pierotti, V., Loring, J.F., Traber, M., Ruland, S., Stokowski, R.S., Huszar, D., and Young, S.G. (1996). Phenotypic analysis of mice expressing exclusively apolipoprotein B48 or apolipoprotein B100. Proc. Natl. Acad. Sci USA 93: 6393-6398.

18. **Véniant, M.**, Ménard, J., Bruneval, P., Morley, S., Gonzales, M.F., and Mullins, J.J. (1996). Vascular damage without hypertension in transgenic rats expressing prorenin exclusively in the liver. J. Clin. Invest. 98: 1966-1970.

19. Ménard, J., Karam, H., **Véniant, M.**, Heudes, D., Bruneval, P. and Clozel, J.P. (1997). Effects of calcium blockade on end-organ damage in experimental hypertension. J. Hypertens. 15: S19-S30

20. **Véniant, M.**, Pierotti, V., Newland, D., Sanan, D.A., Walzem, R.L. and Young, S.G. (1997). Susceptibility to atherosclerosis in mice expressing exclusively apolipoprotein B48 or apolipoprotein B100. J . Clin. Invest. 100: 180-188.

21. Kim, E., Cham, C.M., **Véniant, M.**, Ambroziak, P., and Young, S.G. (1998). Dual mechanisms for the low plasma levels of truncated apolipoprotein B proteins in familial hypobetalipoproteinemia —Analysis of a new mouse model with a nonsense mutation in the apo b gene. J . Clin. Invest : 101: 1468-1477.

22. Borén, J., **Véniant, M.**, and Young, S.G. (1998). Apo-B100-containing lipoproteins are secreted by the heart. J . Clin. Invest : 101: 1197-1202.

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24. Raabe M., Flynn L. M., Zlot C. H., Wong J. S., **Véniant, M.**, Hamilton R. L., and Young, S. G. (1998). Knockout of the abetalipoproteinemia gene in mice: Reduced lipoprotein secretion in heterozygotes and embryonic lethality in homozygotes. Proc. Natl. Acad. Sci USA. 95: 8686-8691

25. Powell-Braxton L., **Véniant, M.**, Latvala R. D., Hirano K-I., Won W.B., Ross J., Dybdal N., Young, S. G, and Davidson N.O. (1998). A mouse model of human familial

hypercholesterolemia: markedly elevated low density lipoprotein cholesterol levels and severe atherosclerosis on a low-fat chow diet. Nature Medicine. 4: 934-938

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27. **Véniant, M.**, Zlot, C.H.,Walzem, R.L., Pierotti, V., Driscoll, R., Dichek, D., Herz, J. and Young, S.G. (1998). Lipoprotein clearance mechanisms in LDL receptor–deficient "Apo-B48-only" and "Apo-B100-only" mice. J . Clin. Invest. 102: 1559-1568.

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37. **Véniant, M.**, Withycombe S and Young S. (2001), ATVB Atherosclerosis susceptibility in chow fed Apoe$^{-/-}$ and Ldlr$^{-/-}$ mice matched for total plasma cholesterol. 10:1567-70.

38. **Véniant, M.**, leBel CP. (2003) Curr.Pharml. Des. Leptin: from animals to humans. 9:811-818.

39. Cozen, AE., Moriwaki, H., Kremen, M., DeYoung, MB., Dichek, HL., Slezicki, KI., Young, SG., **Véniant, M.**, Dichek, DA. (2004) Circulation. Macrophage-targeted overexpression of urokinase causes accelerated atherosclerosis, coronary artery occlusions and premature death. 109: 2129-2135

40. Samuel, VT., Choi, CS., Phillips, TG., Romanelli, AJ., Geisler, JG., Bhanot, S., McKay, R., Monia, B., Shutter, JR., Lindberg, RA., Shulman, GI., **Véniant, M.**. (2006) Diabetes. Targeting Foxo1 in mice using antisense oligonucleotide improves hepatic and peripheral insulin action. 55(7): 2042-2050.

41. Jean DJ Jr., Yuan C., Bercot E.A., Cupples R., Chen M., Fretland J., Hale C., Hungate R.W., Komorowski R., **Veniant M.**, Wang M., Zhang X., Fotsch C. (2007) J Med Chem. 2-(S)-phenethylaminothiazolones as potent, orally efficacious inhibitors of 11 beta-hydroxysteriod dehydrogenase type 1. 50:429-32.

PATENTS

1. Fructose 1,6-BP: "Treatment of Diabetes with Modulators of Fructose 1.6-Bisphosphatase Expression"; US provisional application 60/555,091 (Amgen docket number A-894-P) filed 3/19/04. Inventors Dobie, Bhanot S, **Veniant**-Ellison M, Shutter J, Lindberg R.

2. Forkhead: "Modulation of Forkhead Box 01A Expression" Us application 10/271,074 (Amgen docket number A-829-A) filed 9/26/03. Related PCT, Taiwaon, Thailand, Malta, and Argentina applications also filed. Dobie, Bhanot S, Monia B, McKay R, Geisler J, **Veniant**-Ellison M, Shutter J, Lindberg R.

ORAL COMMUNICATIONS

1. **Véniant M.**, Clozel J.P. (1991). Vascular protection by cilazapril. National Congress of the Arterial Hypertension Society of Mexico; 26-29 May, Mexico City, Mexico.
2. **Véniant M.**, Clozel J.P., Hess P., Wolfgang R. (1991). Ro 40-5967, in contrast to diltiazem and verapamil, does not reduce left ventricular contractility in rats without and with chronic myocardial infarction. Second International Symposium of Calcium Antagonists in Cardiovascular Care, 13-15 February, Basel, Switzerland.
3. **Véniant M.**, Clozel J.P., Fischli W. (1991). Comparative hemodynamic effects of a renin inhibitor, an angiotensin converting enzyme inhibitor and an AII receptor blocker in a sodium depleted guinea pigs. RECARE, 1 February, Strasbourg, France.
4. **Véniant M.**, Clozel J.P., Heudes D., Bruneval P., Ménard J. (1993). Similarité des effets néfastes de l'inhibition de l'enzyme de conversion et du blocage des canaux calciques lents sur le rein sténosé de l'hypertension expérimentale (2K-1C). Differences de leurs actions sur le rein controlatéral. Journées de l'hypertension artérielles, 17-18 décembre, Paris, France.
5. **Véniant M.**, (1993). Effects of Ro 40-5967, a new calcium antagonist, and enalapril on cardiac remodeling and renal changes in 2K-1C renal hypertensive rats. Seminar presentation, 18 may, Blood Unit Western Infirmary Hospital, Glasgow, UK.
6. Whitworth C.E., **Véniant M.**, Firth J.D., Cumming A.D., Mullins J.J. (1994). Role of endothelin in transition from benign to malignant hypertension in transgenic rats. Renal Association October 14-16, London, UK.
7. **Véniant M.**, Karam H., Ménard J., Clozel J.P. (1994). Differences in prevention of end organ damage by converting enzyme inhibition and calcium blockade in 2K-1C and Doca hypertensive rats. American hypertension meeting May 11-14, New York, USA.
8. Whitworth C.E., **Véniant M.**, Firth J.D., Cumming A.D., Mullins J.J. (1995). Increased renal endothelin-1 (ET-1) synthesis does not initiate transition from begnin to malignant

hypertension in transgenic rats. XIIIth International Congress of Nephrology May 14-17, Madrid, Spain.

9. **Véniant, M.,** (1997). Susceptibility to atherosclerosis in mice expressing exclusively apolipoprotein B48 or apolipoprotein B100. May 15, Hopital Broussais, Paris, France.
10. **Véniant, M.** (1997). Susceptibility to atherosclerosis in mice expressing exclusively apolipoprotein B48 or apolipoprotein B100. May 16, College de France, Paris, France.
11. **Véniant, M.** (1997). Susceptibility to atherosclerosis in mice expressing exclusively apolipoprotein B48 or apolipoprotein B100. May 19, Hoffmann La Roche, Basel, Switzerland.
12. **Véniant, M.** (2004). Effect of Foxo 1 inhibition in mice. July 2204, Drug Discovery world summit, San Diego, USA.
13. **Véniant, M.** (2007). Effect of Leptin on Atherosclerosis in *Apoe*$^{-/-}$*Apob*$^{100/100}$*ob*$^{-/-}$ and *Ldlr*$^{-/-}$*Apob*$^{100/100}$*ob*$^{-/-}$ Mice. February 22, 2207, Colombia University, New York, USA.

ABSTRACT PUBLICATIONS

1. Véniant M., Clozel J.P. (1990). Ro 40-5967, in contrast to diltiazem, does not reduce left ventricular function in rats without and with chronic myocardial infarction. J. Mol. Cell. Cardiol.; 22 (suppl IV): S61.
2. Véniant M., Clozel J.P., Fischli W. (1991). Mechanism of the potentiation by angiotensin converting enzyme inhibition of intradermal bradykinin in guinea pig: comparison with renin inhibition and measurement of bradykinin degradation in blood. J. Mol. Cell. Cardiol.; 23 (suppl IV) S60.
3. Eng M., Véniant M., Floege J., Clozel J.P., Fingerle J., Alpers C.E., Johnson R.J. (1992). Angiotensin II-mediated cellular proliferation and extracellular matrix expansion require the presence of hypertension. J. Am. Society of nephrology, 3 (vol 3): 585, 25th meeting 15-18 November, Baltimore, USA.
4. Véniant M., Clozel J.P., Ménard J. (1993). Worsening of the lesions of the clipped kidney in 2 kidney-1 clip rats during ACE inhibition is explained by blood pressure fall. J. Hypertens. 6th European meeting of hypertension, Milan, Italy.
5. Véniant M., Heudes D., Ménard J., Clozel J.P. (1993). Comparison of the changes in large artery structure following the same blood pressure decrease using two different antihypertensive drugs. 6th European meeting of hypertension, Milan, Italy.
6. Geisler J., Banhot S., McKay R., Shutter J., Monia B., Lindberg R., Veniant M. (2004) Effect of foxo 1 antisense oligonucleotide (ASO) therapy in mice. Keystone symposia, Banf, Canada.
7. Samuel VT., Choi CS., Phillips TG., Romanelli AJ., Geisler JG., Bhanot S., McKay RA., Monia BP., Shutter JR., Lindberg RA., Shulman GI., Veniant M. (2005) Targeting foxo1 in mice using antisense oligonucleotide improves hepatic and peripheral insulin action. American Diabetes Association, San Diego, CA
8. Geisler JG., Veniant M., Bhanot S., Monia BP., Lindberg RA., McKay RA., Shutter JR. (2005) 98% reduction in liver fructose 1, 6 bisphosphatase is insufficient to lower fasting blood glucose levels in mice. American Diabetes Association, San Diego, CA
9. Samuel VT., Choi CS., Phillips TG., Romanelli AJ., Geisler JG., Bhanot S., McKay RA., Monia BP., Shutter JR., Lindberg RA., Shulman GI., Veniant M. (2005)

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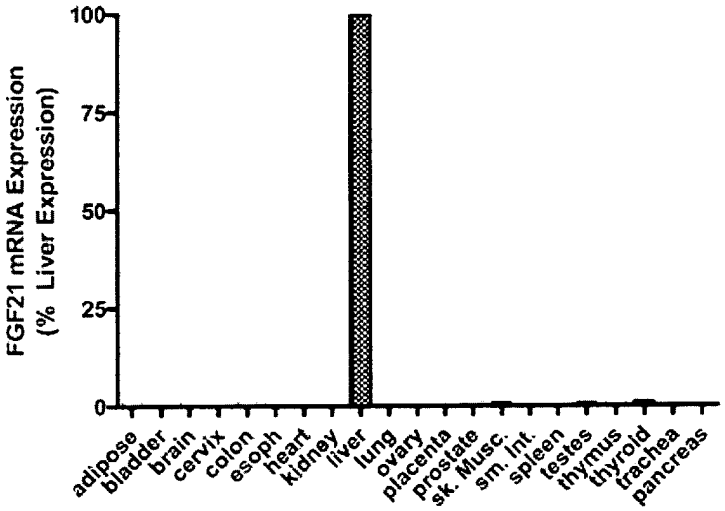
10. Hale C., Komorowskin R., Fotsch C., Emery M., Lindberg R., Wang M. and Veniant M. (2006) Inhibition of 11β-HSD1 in Mice with Diet Induced Obesity Improves glucose tolerance and insulin sensitivity. ADA, Washinghton DC

11. Lu S.C., Xu J., Chinookoswong N., Veniant M., Gegg C., Liu S., Chang D., Wang T., Steavenson S., Chen C., Brankow D., Lindberg R., and Gu W (2006). Immunoneutralization of Peripheral Acyl-Ghrelin with a Monoclonal Antibody in Diet Induced Obese Mice. Endocrinology, Boston, MA

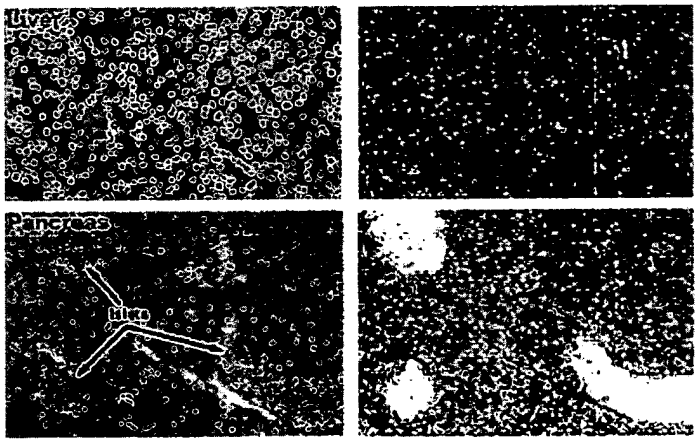
12. McCormick J., Kaufman S., Witkosky J., Stanislaus S., Lofing J., Lindberg R. and Veniant M. (2006) The effect of leptin versus food restriction on lipid metabolism and atherosclerosis in *Apoe*$^{-/-}$*Apob*$^{100/100}$*ob*$^{-/-}$ and *Ldlr*$^{-/-}$*Apob*$^{100/100}$*ob*$^{-/-}$ mice. International Symposium of atherosclerosis. Roma, Italy.

APPENDIX B

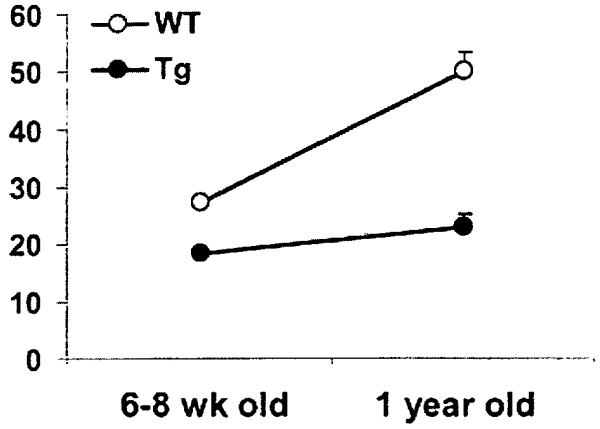
Human

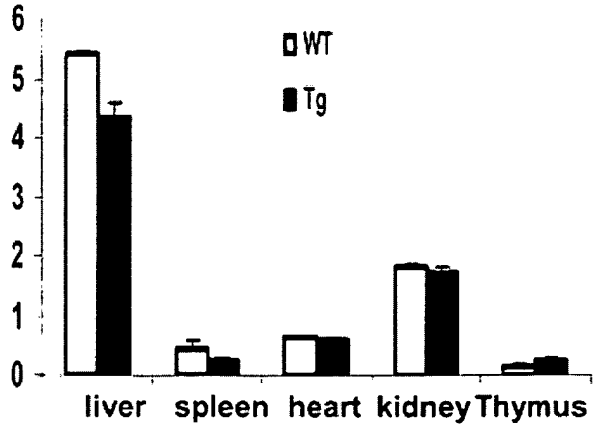


Mouse

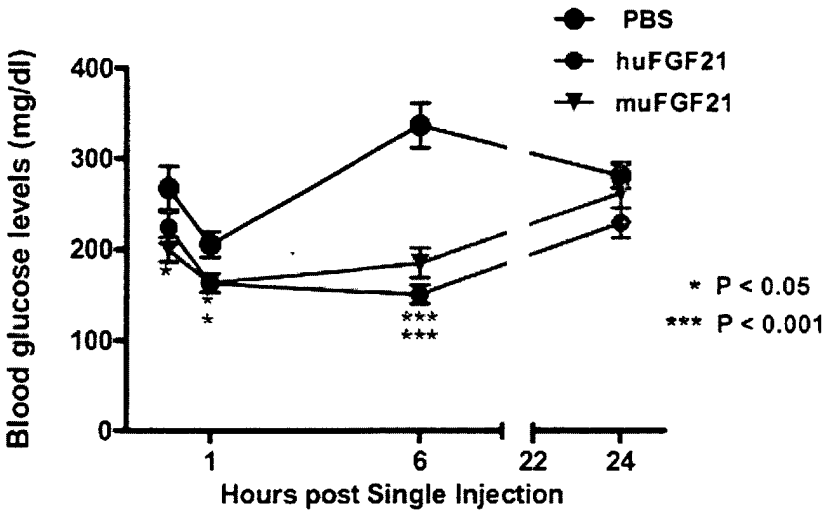


APPENDIX B


60
50
40
30
20
10
0
WT
Tg
6-8 wk old
1 year old

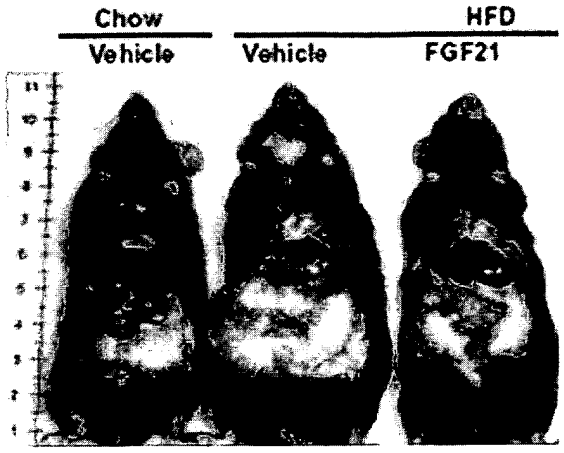

6
5
4
3
2
1
0
WT
Tg
liver
spleen
heart
kidney
Thymus

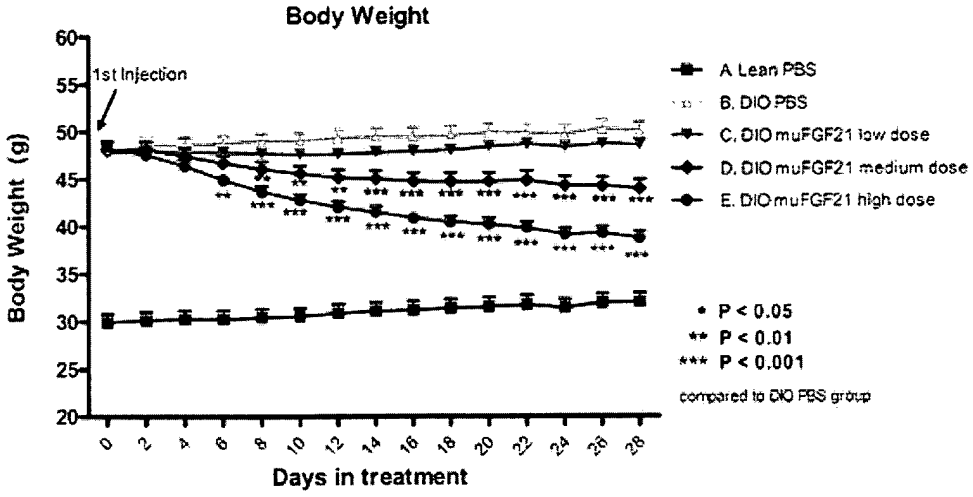
APPENDIX B


PBS
huFGF21
muFGF21
Blood glucose levels (mg/dl)
400
300
200
100
0
1
6
22
24
Hours post Single Injection
* P < 0.05
*** P < 0.001

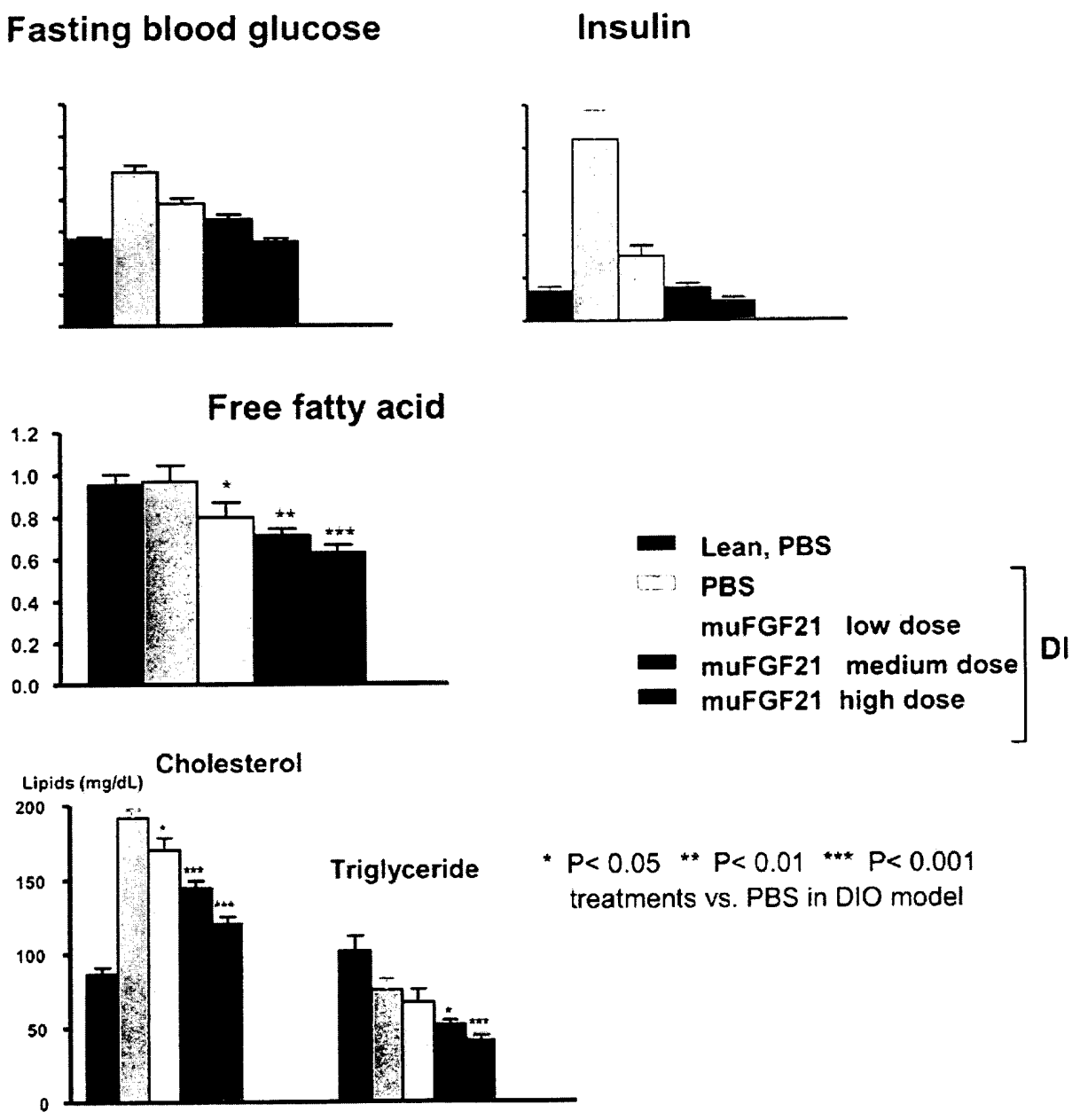

PBS
huFGF21
muFGF21
Change in Body Weight (g)
0.4
0.2
0.0
-0.2
-0.4
* P < 0.05

APPENDIX B

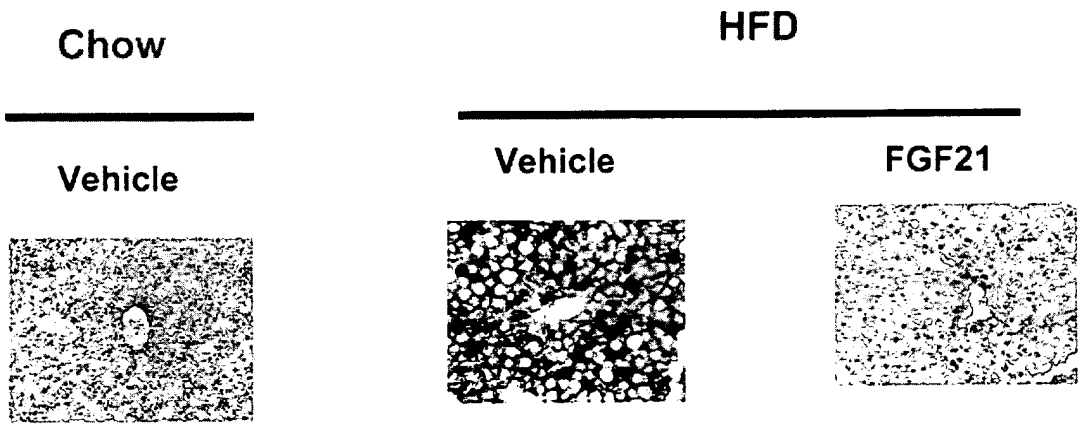

Chow
HFD
Vehicle
Vehicle
FGF21


Body Weight
1st Injection
Body Weight (g)
Days in treatment
A. Lean PBS
B. DIO PBS
C. DIO muFGF21 low dose
D. DIO muFGF21 medium dose
E. DIO muFGF21 high dose
* P < 0.05
** P < 0.01
*** P < 0.001
compared to DIO PBS group

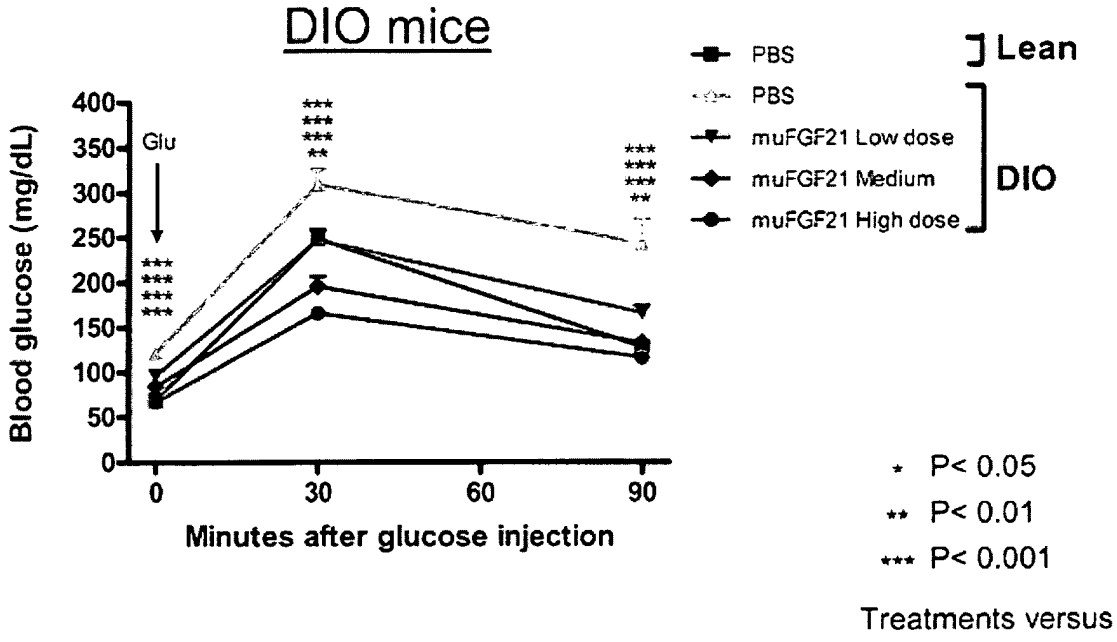
APPENDIX B

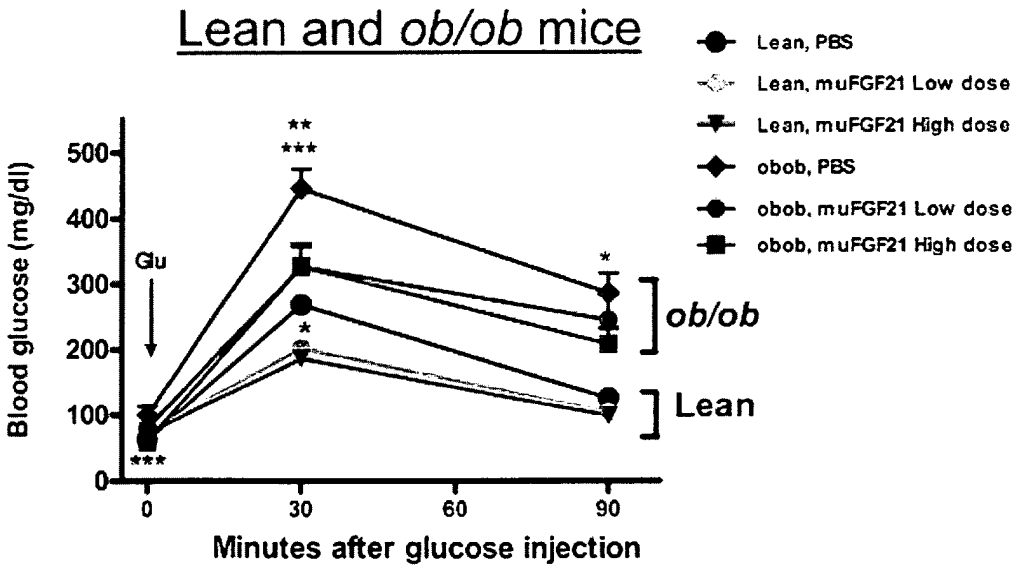

Fasting blood glucose
Insulin
Free fatty acid
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
**
***
Lean, PBS
PBS
muFGF21 low dose
muFGF21 medium dose
muFGF21 high dose
DI
Cholesterol
Lipids (mg/dL)
200
150
100
50
0
Triglyceride
* P< 0.05 ** P< 0.01 *** P< 0.001
treatments vs. PBS in DIO model

APPENDIX B

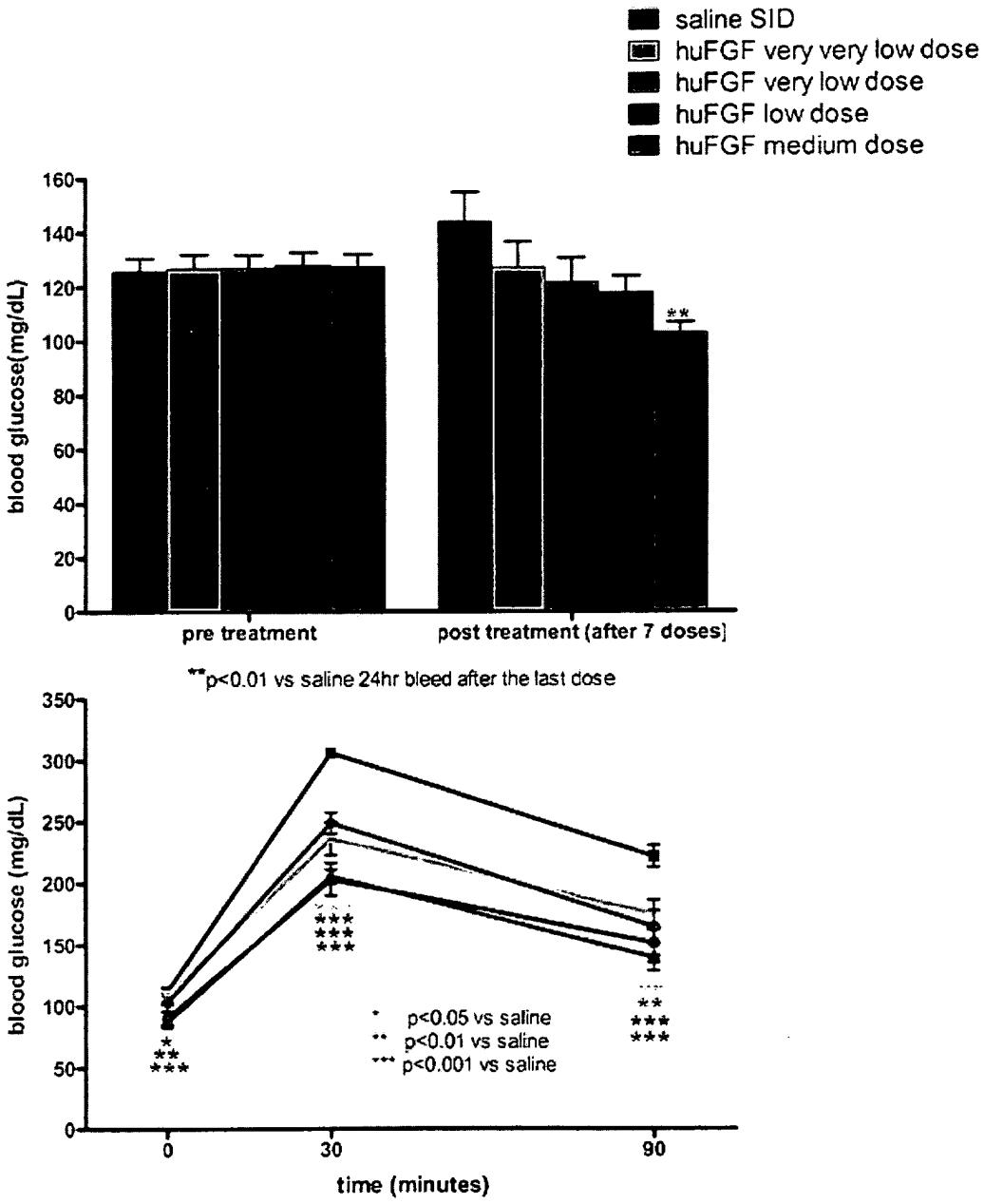


APPENDIX B


DIO mice
PBS
PBS
muFGF21 Low dose
muFGF21 Medium
muFGF21 High dose
Lean
DIO
Blood glucose (mg/dL)
Glu
Minutes after glucose injection
0
30
60
90
* P< 0.05
** P< 0.01
*** P< 0.001
Treatments versus


Lean and ob/ob mice
Lean, PBS
Lean, muFGF21 Low dose
Lean, muFGF21 High dose
obob, PBS
obob, muFGF21 Low dose
obob, muFGF21 High dose
ob/ob
Lean
Blood glucose (mg/dl)
Glu
Minutes after glucose injection

APPENDIX B


saline SID
huFGF very very low dose
huFGF very low dose
huFGF low dose
huFGF medium dose
blood glucose(mg/dL)
160
140
120
100
80
60
40
20
0
**
pre treatment
post treatment (after 7 doses)
**p<0.01 vs saline 24hr bleed after the last dose
blood glucose (mg/dL)
350
300
250
200
150
100
50
0
0
30
90
time (minutes)
* p<0.05 vs saline
** p<0.01 vs saline
*** p<0.001 vs saline